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December 1, 2009
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NEIHS/NTP
NTP Center for the evaluation of Risks to Human Reproduction (CERHR)
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Room 2154/Mail Drop K2-04
Morrisville, NC 27560

By email: Thayer@niehs.nih.gov

Dear Dr. Thayer and Expert Panel,

The Weston A. Price Foundation, a non-profit nutrition information foundation, has expressed concerns about the dangers of soy infant formula since its founding in 1999. The Foundation has submitted testimony at FDA meetings and in fact, met with FDA officials several years ago. To date, these concerns have been completely ignored.

The Foundation has received many letters, phone calls and emails from heartbroken parents reporting numerous serious health problems in their soy-fed children—breast development and early puberty in girls, abnormal size of reproductive organs in boys (either very large or very small), severe behavior and learning problems, thyroid disorders, weight gain, reproductive problems and digestive disorders. From therapists working with autistic children we learn that a very high percentage of these children began life on soy formula—in some groups as high as 100 percent of autistic children received soy formula as infants.

Numerous studies link soy protein to digestive distress, thyroid damage, reproductive problems, infertility, ADD/ADHD, dementia, even heart disease and cancer.

FDA's own database contains over 200 citations on the toxicity of isoflavones in soy (http://vm.cfsan.fda.gov/~djw/pltx.cgi?QUERY=soy). Many recent studies link exposure to even small amounts of isoflavones in utero and infancy to a variety of pathologies including behavioral problems and altered sexual behavior.

In addition, these plant-based estrogens can act as thyroid inhibitors in sensitive individuals.

Figure 1: PHYTOESTROGENS IN DIETS OF INFANTS AND ADULTS

	Average Isoflavone Intake	**Isoflavones per Kg of Body Weight***
Japan (1996 survey)	10 mg	0.17 mg
Japan (1998 survey)	25 mg	0.42 mg
Japan (2000 survey)	28 mg	0.47 mg
In Japanese women receiving adequate iodine, causing thyroid suppression after three months	38 mg	0.60 mg
In American women, causing hormonal changes after one month	45 mg	0.75 mg
FDA recommended amount for adults	25 mg	42 mg
In children receiving soy formula	**38 mg**	**6.25 mg**

* Assumed 60 kg for adults, 6 kg for infants

The simple calculation in Figure 1 shows that an infant on soy formula receives, on a body-weight basis, approximately ten times the amount of isoflavones that have caused thyroid suppression after three months in Japanese women receiving adequate iodine, and eight times the amount that caused hormonal changes in American women after one month.

Soy formula also contains high levels of aluminum, fluoride, free glutamic acid and manganese. Manganese is particularly harmful to the brains of vulnerable infants; the symptoms of manganese toxicity are identical to those of autism.

Extremely high levels of oxalates in soy explain the many digestive problems found in studies and reported to us by parents.

We believe that soy protein isolate (SPI), the major ingredient in soy formula, does not have GRAS status, and we have been unable to ascertain whether formula makers have obtained pre-market approval for the addition of SPI to infant formula.

Educated parents are now avoiding soy formula for their infants; however, we are concerned about the allowance of soy formula in the WIC program and other projects aimed at low-income families. Hispanics, blacks and other minorities are thus targeted and more at risk from soy formula usage.

Three foreign governments have issued warnings about soy. In 2005, the Israeli Health Ministry warned its citizens that babies should not receive soy formula, that children age 18 and under should consume soy foods or soy milk no more than once per day to a maximum of three times per week and that adults should exercise caution because of adverse effects on fertility and increased breast cancer risk.

In 2006, the French Food Agency (AFSSA) announced tough new regulations that will require manufacturers to improve the safety of soy infant formula and to put warning labels on packages of soy foods and soy milk.

In 2007, the German Federal Institute for Risk Assessment warned that babies should not be given soy infant formula "without clear, concrete medical reasons" and that adults should be wary of excess soy food and soy supplement consumption because they offer no proven health benefits and may pose health risks.

The fact that the U.S. government has not issued a warning about soy infant formula can only be explained by the powerful influence of the soy lobby in this country.

It is time for FDA to exercise the cautionary principle and issue a strong warning against soy infant formula before more children are damaged. Soy formula should be removed from the WIC program and subjected to regulations stipulating availability only through a doctor's prescription. The formula industry should be enjoined to return meat-based formulas to the market for children with milk allergies.

I look forward to presenting this testimony at your meeting December 16.

Sincerely yours,

Signature Redacted

Sally Fallon Morell
President

REFERENCES
STUDIES SHOWING ADVERSE EFFECTS OF ISOFLAVONES

1953
Cheng C and others. Estrogenic Activity of Isoflavone Derivatives Extracted and Prepared from Soybean Meal. *Science* 1953;118:164-5. Feeding 2.5 or 5.0 mg of either genistein or genistin per day to the mouse resulted in increased uterine weights.

1954
Carter M and others. Effect of Genistin on Reproduction of the Mouse. *J Nutr* 1954;55:639. Exposure to the phytoestrogen genistin caused significant advancement of the vaginal opening and a decrease in the number of litters born.

1956
Matrone G and others. Effect of Genistin on Growth and Development of the Male Mouse. *J Nutr*, 1956, 235-240. "The evidence presented indicates that genistin at certain dose levels has a detrimental effect on survival, growth rates and spermatogenesis in mice. . . the higher dose appeared to be lethal. It appears that genistin in relation to its estrogenic activity has a greater depressing effect on growth than does stilbestrol."

1962
Wong E. Estrogenic Activity of Red Clover Isoflavones and Some of Their Degradation Products. *J Endocrinology* 1962;24:341-348. This was a comparative in vivo (mice on uterine effects) study of the estrogenic effects of several red clover isoflavones "The bioassays showed that genistein was the most potent of the isoflavones."

1963
Magee AC. Biological Responses of Young Rats Fed Diets Contain Genistin or Genistein. *J Nutr* 1963;80:151. A dietary level of 0.5% genistin or genistein resulted in significant decreases in weight gain and in the weights of kidneys and spleen.

1963
Noteboom and Gorski. Estrogenic Effects of Genistein and Coumestrol Diacetate. *Endocrinology* 1963;73:736-9. "It is quite likely that plant estrogens perform the same function as estradiol in triggering anabolic responses. The results of these experiments indicate that certain of the nonsteroidal estrogenic compounds are capable of stimulation of labelled precursors into protein, lipid and ribonucleic acid in the cells of the rat uterus."

1966
Folmon Y and others. The interaction in the Immature Mouse of Potent Estrogens with Coumestrol, Genistein and other Utero-Vaginotropic Compounds of Low Potency. *J Endrocrin* 1966;34:215-225. Phytoestrogens such as genistein are said to be of "weak" potency. This study found that sometimes these estrogens were additive at very small doses and appeared to be antagonistic at higher doses. "Genistein gave a steep dose-response curve with high responses (uterus weight near 45 grams) typical of the most potent estrogens."

1967
Braden and others. The oestrogenic activity and metabolism of certain isoflavones in sheep. *Australian Journal of Agricultural Research* 1967, 18:335-348. "Some plants that are commonly grazed nevertheless contain substances that are harmful to the animals ingesting

them and one group of such compounds (phyto-estrogens) can cause reproductive disorders in females."

1972
Shutt DR. Steroid and Phytoestrogen Binding to Sheep Uterine Receptors in Vitro. *J Endocrin* 1972;52:299-305. Phytoestrogens were found to compete with estradiol for binding sites. "A full estrogenic response is elicited only when they are given in repeated frequent doses, which may be necessary to maintain a high blood concentration."

1972
Rackis JJ. Biological Effects. *Soy Beans: Chemistry and Technology*, AK Smith and SK Circle, eds. Avi Publishing, Inc. Westport, CT, 1972. This is an industry text book that lists a number of established toxic effects from soybeans, with copious reference lists for each chapter.

1975
Farnsworth NR and others. Potential Value of Plants as Anti-fertility Agents. *J Pharm Sci*. "Phytochemical interest in plant estrogens…increased in the 1950s due to the recognition that infertility in animals and humans could follow excessive ingestion of plants rich in estogenic activity" Genistein and Daidzein were identified in soybeans "A large reduction in sperm numbers was observed in prolonged grazing of sheep in clover pasture'…." Genistein has a remarkable structural similarity to DES."

1976
Chemical Carcinogens, MF Beringer, ed. American Chemical Society, pp 658 – 664. "The younger the animal the more susceptible it is to the action of estrogens, as it frequently is to other carcinogens."

1976
Leopold AS and others. Phytoestrogens: Adverse effects on reproduction in California Quail. *Science*, 1976 Jan 9;191(4222): 98-100. During dry years, phytoestrogens, including genistein, are produced in the leaves of stunted desert annuals. When ingested by California quail, these compounds apparently inhibit reproduction and prevent the production of young that would not have adequate food. In a wet year, forage grows vigorously and phytoestrogenic substances are largely absent. Quail then breed prolifically and the abundant seed crop carries the enlarged population through the winter.

1976
Kimura S and others. Development of malignant goiter by defatted soybean with iodine-free diet in rats. *Gann* 1976, 67:763-765. Iodine-deficient rats fed defatted soybean for 6 to 12 months developed enlarged goiters and malignant thyroid tumors. Thyroid enlargement was inhibited with the addition of small amounts of iodine to the diet.

1976
Shutt DR. The Effects of Plant Estrogens in Animal Reproduction. *Endeavour* 1976:110-113. "In high concentrations, a weak plant estrogen can exert a significant estrogenic effect in the animal and can product hormonal imbalance. . . when high blood concentrations are maintained, they can exert a maximal estrogenic effect. . . From the wider viewpoint of evolution, it is interesting that compounds have evolved in plants that not only give the

plant some protection from pathogens, but also reduce fertility of animals ingesting the plant."

1976
Lindner HR. Occurrence of Anabolic Agents in Plants and their Importance. *Environment Quality Supplement* 1976;5:151-158. "Coumestrol and genistein stimulate estradiol in stimulating macromolecular changes in the uterus. The biological effects of clover estrogens responsible for fertility impairment appear to be multiple."

1977
Hormonally Active Substances in Foods: A Safety Evaluation. Report #66. Council for Agricultural Science and Technology, Report #66 1977 Mar;66. "Estrogens are essential for life. They occur naturally. Small quantities are essential for reproduction and other functions. Large doses are harmful (p 1). . . The Delaney Clause states in relevant part that no food additive shall be deemed safe if appropriate tests show it induces cancer in man or animal (p 3). . . Whenever persons are put at risk, the relevant principle involved is that of 'informed consent.' That is, the persons concerned should ideally have an appreciation of the risks associated with the particular act or situation in question so they can make intelligent choices. The zero tolerance concept implicit in the Delaney Clause is not dead in the area of regulationof chemicals."

1978
Martin PM and others. Phytoestrogen interaction with estrogen receptors in human breast cancer cells. *Endocrinology* 1978 Nov;103(5):1860-7. Phytoestrogens "translocate the cytoplasmic estrogen receptor and bind to unfilled nuclear estrogen receptors in whole cells. Bound nuclear receptors are then processed in a manner similar to estradiol in a step which rapidly decreases total cellular estrogen receptors. The phytoestrogens are also biologically active; they can markedly enhance tumor cell proliferation."

1980
Drane HM and others. Oestrogenic activity of soya-bean products. *Food Cosmetics and Technology* 1980 Aug;18(4):425-427. Sixteen samples of soya-containing products were examined after the commercial mouse diet was found to have estrogenic effects in laboratory mice, and compared with the effects of DES on the weight of the mouse uterus. All samples demonstrated estrogenic activity. The researchers attributed the effects as equivalent to 16 ppb and 24 ppb DES in the two samples of human food used.

1980
Mathieson R and Kitts W. Binding of Phytoestrogen and Estradiol 17-B by Cytoplasmic Receptors in the Pituitary Gland and Hypothalamus in the Ewe. *J Endocrinol* 1980;85:317-25. "These results suggest that phytoestrogens can interfere with the normal estrogen feedback mechanisms with respect to release of gonadotropin in the ewe. . . although most studies into the effects of phytoestrogens have concentrated on changes in the reproductive tract, there are indications that they interfere with the hormone balance between the ovaries and the hypothalamo-adenohypophysical system. . . ewes on phytoestrogens have shown follicular abnormalities such as numerous small follicles, deficient antrum formation and signs of early atresia. . . it is possible that the permanent changes brought about by phytoestrogens in the brain are a result of these compounds interacting with estrogen receptors in this tissue, and subsequently influencing the re-synthesis or replenishment of

cyto-plasmic estrogen receptors. . . phytoestrogens can interfere with the delicate feedback mechanisms involved in the release of the gonadotrophins."

1985
Jones and others. Naturally Occurring Estrogens in Food--A Review. *Journal of Food Additives and Contamination* 1985;2(2):73-106. That estrogen compounds in plants "induce estrus in immature animals and interfere with normal reproductive processes has been known for more than half a century. Consideration should be taken of any medium or long-term changes in dietary habits which might be expected to increase the intake of such phytoestrogens. The increasing use of vegetable proteins in general, and in particular introduction of soy milk products for infant feeding, are two such examples."

1985
Setchell KD. Non Steroidal Estrogens of Dietary Origin. *Estrogens in the Environment*, John A McLaughlin, ed. Elsevier, 1985:69-83. "Since as little as 8 mg of genistein and 10 mg of daidzein are sufficient to initiate uterotrophic effects in mice, it is not surprising that the relatively large amounts of isoflavones present in soy protein will readily explain the previously observed estrogenic effects in animals. . . . The effects of plant estrogens in man should, however, be of some concern since the newborn infant will be subject to chronic exposure to soya milk, in some cases for up to two years. . . this situation could be considered analogous to sheep grazing on clover."

1987
Hughes CI Jr. Effects of phytoestrogens on GnRH-induced luteinizing hormone secretion in ovariectomized rats. *Reprod Toxicol* 1987-88;1(3):179-81. "The dose potency of genistein appears to be approximately 1/10 that of E2 [estradiol-17 beta] in this system. Phytoestrogens acutely perturb reproductive and neuroendocrine function."

1987
Setchell, KD and others. Dietary estrogens - a Probable Cause of Infertility and Liver Disease in captive cheetahs. *Gastroenterology* Aug 93(2):225-233. Captive adult cheetahs consuming approximately 50 mg soy isoflavones per day from soy-based feed develop reproductive failure and liver disease. When chicken-based feed was substituted for soy-based feed, liver function improved. ". . . the relatively high concentrations of phytoestrogens from soybean protein present in the commercial diet fed to captive cheetahs in North American zoos may be one of the major factors in the decline of fertility and in the etiology of liver disease in this species. The survival of the captive cheetah population could depend upon a simple change of diet by excluding exogenous estrogens."

1989
Kaldas RS and Hughes CL Reproductive and General Metabolic Effects of Phytoestrogens in Mammals. *Reprod Toxicol* 1989;3:81-89 ". . . these compounds might have a role in the evolutionary success of herbivores, perhaps making the difference between survival and extinction of species. We hypothesise that phytoestrogen-induced physiologic and behavioral effects are significant factors in the reproductive and therefore evolutionary success of species.

1989
Markovitz J and others. Inhibitory Effects of the Tyrosine Kkinase Inhibitor Genistein on

Mammalian DNA Topoisomerase II. *Cancer Res* 1989 Sep 15;49(18):5111-7. Genistein stimulates double strand DNA breaks.

1989
Jones AE. Development and Application of High Performance Chromatographic Method for the Analysis of Phytoestrogens. *Jour Sci Food Agric* 1989;46:157-164. "It should be emphasised that the effects of long-term low level exposure are unknown. . . . Vegetarians, vegans and those relying on 'health' food preparations from alfalfa, legumes or soya in particular would appear to be likely to regularly consume very much higher levels of estrogens than those estimated for the population at large."

1990
Yamashita Y and others. Induction of Mammalian Topisomerase II Dependent DNA Cleavage by Nonintercalative Flavonoids, Genistein and Orobol. *Biochem Pharmacol* 1990 Feb 15;39(4):737-44. Genistein induced DNA cleavage in vitro.

1991
Y Ishizuki and others. The Effects on the Thyroid Gland of Soybeans Administered Experimentally in Healthy Subjects. *Nippon Naibunpi Gakkai Zasshi* 1991, 767: 622-629. Feeding 30 grams (2 tablespoons) roasted pickled soybeans per day for three months to healthy adults receiving adequate iodine intake caused thyroid suppression, especially in the elderly. Hypometabolic symptoms (malaise, constipation, sleepiness) and goiters appeared in half the younger subjects (mean age of 29) and half the older subjects (mean age 61). The symptoms disappeared 1 month after the cessation of soybean ingestion. "These findings suggested that excessive soybean ingestion for a certain duration might suppress thyroid function and cause goiters in healthy people, especially elderly subjects." Note that 30 grams per day was considered "excessive" by these Japanese researchers.

1991
Pelissero C and others. Estrogenic Effect of Dietary Soy Bean Meal on Vitellogenesis in Cultured Siberian Sturgeon Acipenser baeri. *Gen Comp Endocrinol* 1991 Sep;83(3):447-57 83:447-457. Sturgeon fed a diet high in isoflavones from soybeans had significantly higher levels of plasma vitellogenin. Vitellogenin is a biomarker for estrogenic effects.

1991
O'Dell TJ and others. Long-term Potentiation in the Hippocampus is Blocked by Tyrosine Kinase Inhibitors. *Nature* 1991 Oct; 353(6344):558-60. Long-term potentiation (LTP) in the hippocampus is thought to contribute to memory formation. Tyrosine kinase inhibitors (such as genistein) block LTP.

1991
Atluru S and Atluru D. Evidence that Genistein, a Protein-tyrosine Kinase Inhibitor, Inhibits CD28 Monoclonal-antibody-stimulated Human T cell proliferation. *Transplantation* 1991 Feb;51(2):448-50. Genistein blocks the production of T cells needed for the immune system. The authors conclude: " . . . that genistein is a powerful immunosuppressive agent. . ." and suggest that it has a potential use in the treatment of allograft rejection.

1992
Bulletin de L'Office Federal de la Santé Publique, No 28, July 20, 1992. The Swiss health service estimates that 100 grams of soy protein provides the estrogenic equivalent of the

contraceptive pill. One hundred grams of soy protein contains about 97 g total isoflavones according to USDA-Iowa State University Database on the Isoflavone Content of Foods 1999.

1992
Mayr U. Validation of Two In Vitro Test Systems of Estrogenic Activities with Zearelenone, Phytoestrogens and Cereal Extracts. *Toxicology* 1992;72:135-149. "Ingestion of these compounds causes diseases of the reproductive system, reversible and irreversible infertility and abnormal fetal development in all kinds of farm animals. Furthermore, an inherent health risk to man cannot be excluded." This paper contains graphs showing the crossover of phytoestrogens from estrogenic to anti-estrogenic to toxic.

1992
Traganos F and others. Effects of genistein on the growth and cell cycle progression of normal human lymphocytes and human leukemic MOLT-4 and HL-60 cells. *Cancer Res* 1992 Nov 15;52(22):6200-8. The results suggest that genistein "is expected to be a strong immunosuppressant."

1993
McCabe MJ Jr and Orrenius S. Genistein induces apoptosis in immature human thymocytes by inhibiting topoisomerase-II. *Biochem Biophys Res Commun* 1993; 194(2):944-50. The toxicity of genistein on human thymus cells was investigated. "Genistein induced marked chromatin fragmentation indicative of apoptosis in human thymocyte cultures."

1993
Nicklas RB and others. Odd chromosome movement and inaccurate chromosome distribution in mitosis and meiosis after treatment with protein kinase inhibitors. *J Cell Sci* 1993 Apr;104 part 4:961-73. Genistein, a protein kinase inhibitor, caused errors in chromosome orientation from grasshopper spermatocytes.

1994
Cassidy A and others. Biological Effects of a Diet of Soy Protein Rich in Isoflavones on the Menstrual Cycle of Premenopausal Women. *Am J Clin Nutr* 1994 Sep;60(3):333-340 Six women with regular menstrual cycles were given 60 grams soy protein containing 45 mg isoflavones daily. After one month, all experienced delayed menstruation. Luteinizing hormone and follicle-stimulating hormone were significantly suppressed. The effects were similar to those of tamoxifen, an antiestrogen drug. Regular menstruation did not resume until 3 months following the cessation of soy protein consumption.

1994
Packer AI and others. The ligand of the c-kit receptor promotes oocyte growth. *Dev Biol* 1994 Jan;161 (1):194-205. "In the presence of genistein, many of the follicles became disorganized and the oocytes became partially denuded. . . . There also appeared to be less granulosa cell proliferation compared to the control follicles." This statement appeared in the body of the report, not in the abstract.

1994
Watanabe S and others. Hepatocyte Growth Factor Accelerates the Wound Repair of Cultured Gastric Mucosal Cells. *Biochem Biophys Res Comm* 1994;199(3). Genistein

retarded the repair of gastric mucosal cells, suggesting that genistein may retard the healing of gastric ulcers.

1994
Setchell KD and others. Nonsteroidal estrogens of dietary origin: possible roles in hormone-dependent disease. *Am J Clin Nutr* 1984 Sep;40:569-78. Equol is a breakdown product of phytoestrogens which shows up in the urine of individuals who eat soy. However, some subjects are unable to breakdown phytoestrogens and equol does not show up in their urine.

1994
Santti R and others. Developmental estrogenization and prostatic neoplasia. *Prostate* 1994;24(2):67-78. Evidence indicates that estrogen exposure during development may initiate cellular changes in the prostate which would require estrogens and/or androgens later in life for promotion of prostatic hyperplasia or neoplasia. ". . . the critical time for estrogen action would be during the development of the prostatic tissue. We further suggest that estrogen-sensitive cells may remain in the prostate and be more responsive to estrogens later in life or less responsive to the normal controlling mechanisms of prostatic growth." In other words, exposure of the developing male child to phytoestrogens in soy may make him more susceptible to prostate cancer later in life.

1995
Keung WM. Dietary estrogenic isoflavones are potent inhibitors of B-hydroxysteroid dehydrogenase of P testosteronii. *Biochem Biophys Res Commun* 1995 Oct 24; 215(3):1137-1144. The isoflavones diadzein, genistein, biochanin A and formononetin were found to inhibit enzymes that produce steroid hormones critical to reproductive and neurological function, particularly hormones that produce testosterone.

1995
Makela SI and others. Dietary Soybean May Be Antiestrogenic in Male Mice. *J Nutr* 1995 Mar;125(3):437-45. Soy isoflavones were found to have antiestrogenic action in male mice.

1995
Makela SI and others. Estogen-specific 17 beta-hydroxysteroid oxidoreductase type 1 (E.C.1.1.1.62) as a possible target for the action of phytoestrogens. *Proc Soc Exp Biol Med* 1995 Jan;208(1):51-9. Effects of dietary estrogens are similar to those observed in women taking tamoxifan and indicate that soy foods have the potential to disrupt the endocrine system.

1995
Woodhams DJ. Phytoestrogens and parrots: The anatomy of an investigation. *Proceedings of the Nutrition Society of New Zealand.* 1995, 20:22-30. Observations in aviaries and in handrearing of parrots with bird-baby food were associated with parrot infertility, premature sexual maturation and in some cases acute symptoms causing death. It was noted that soy protein and/or soy meal were a constant ingredient in all the diets used. This triggered an investigation into the literature on the toxic effects of processed soy products. The first source consulted was *Soy Beans: Chemistry and Technology* by Smith and Circle, an industry text book published in 1972 that clearly listed a number of established toxic effects with copious reference lists for each chapter.

1995
Irvine C and others. The Potential Adverse Effects of Soybean Phytoestrogens in Infant Feeding. *New Zealand Medical Journal*. 1995 May 24:318. "Exposure to estrogenic compounds may pose a developmental hazard in infants. . . particularly to the reproductive system. . . Neonates are generally more susceptible than adults to perturbations of the sex steroid milieu.

1995
Robertson IGC. Phytoestrogens: Toxicology and Regulatory Recommendations. *Proc Nutr Soc of NZ* 1995;20:35-42. "Concerns have been expressed about possible adverse effects, particularly to the foetal-neonatal nervous and reproductive system. Adverse effects may occur by inhibition of the enzyme which converts the relatively impotent estrone to the much more potent oestradiol and by occupying the estrogen receptor resulting in antagonism of the naturally produced oestradiol. Adequate oestradiol is necessary for the imprinting and development of many physical, physiological and behavioural characteristics during the neonatal period and infancy. Infants on soy-based formula have been identified as a high risk group because the formula is the main source of nutrient, and because of their small size and developmental phase. Infants absorb phytoestrogens and have a calculated daily dietary intake (per kg) 3-6 times that shown to have physiological effects on women. . ."

1996
Petrakis NL and others. Stimulatory influence of soy protein isolate on breast secretion in pre-and postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 1996 Oct;5(10):785-794. Twenty-four normal pre- and postmenopausal white women, ages 30 to 58 were studied for one year. During months 4-9, the women ingested 38 g soy protein isolate containing 38 mg genistein. Seven of the 24 women developed epithelial hyperplasia during the period of soy feeding, a condition that presages breast cancer. The authors noted that "the findings did not support our a priori hypothesis" that soy protected Asian women against breast cancer. "Instead, this pilot study indicates that prolonged consumption of soy protein isolate has a stimulatory effect on the pre-menopausal female breast, characterised by increased secretion of breast fluid, the appearance of hyperplastic epithelial cells and elevated levels of plasma estradiol. These findings are suggestive of an estrogenic stimulus from the isoflavones genistein and diadzein contained in soy protein isolate."

1997
Dees C and others. Dietary estrogens stimulate human breast cells to enter the cell cycle. *Environ Health Perspect* 1997 Apr;105 (Suppl 3):633-636. Dietary estrogens were found to increase enzymatic activity leading to breast cancer. "Our findings are consistent with a conclusion that dietary estrogens at low concentrations do not act as anti-estrogens, but act like DDT and estradiol to stimulate human breast cancer cells to enter the cell cycle."

1997
Kulling SE and Metzler M. Induction of Micronuclei, DNA Strand Breaks and HPRT mutations in cultured Chinese hamster V79 cells by the phytoestrogen coumoestrol. *Food Chem Toxicol* 1997 Jun; 35(6):605-13. Coumoestrol and genistein caused DNA strand breakage in cultured hamster cells.

1997
Wang C and Kurzer MS. Phytoestrogen concentration determines effects on DNA synthesis

in human breast cancer cells. *Nutr Cancer* 1997;28(3):236-47. Although high levels of isoflavones inhibited DNA synthesis in human breast cancer cells, low levels of genistein and related compounds. . . induced DNA synthesis 150-235%. "The current focus on the role of phytoestrogens in cancer prevention must take into account the biphasic effects observed in this study, showing inhibition of DNA synthesis at high concentrations but induction at concentrations close to probable levels in humans."

1997
Connolly JM and others. Effects of dietary menhaden oil, soy, and a cyclooxygenase inhibitor on human breast cancer cell growth and metastasis in nude mice. *Nutr Cancer* 1997;29(1):48-54. Phytoestrogens at levels close to probable levels in humans were found to stimulate cellular changes leading to breast cancer.

1997
Wang C and Kurzer MS. Phytoestrogen concentration determines effects on DNA synthesis in human breast cancer cells. *Nutr Cancer* 1997;28(3):236-47. Soy intake caused larger mammary fat pad tumors to occur in mice. Soy feeding appeared to suppress enzymes protective of breast cancer.

1997
Anderson D and others. Effect of various genotoxins and reproductive toxins in human lymphocytes and sperm in the Comet assay. *Teratog Carcinog Mutagen* 1997;17(1):29-43. Human sperm exposed to the phytoestrogen diadzein had reduced DNA integrity. "The integrity of DNA is necessary not only for the noncancerous state, but also for the accurate transmission of genetic material to the next generation."

1997
Rao CV and others. Enhancement of experimental colon cancer by genistein. *Cancer Res* 1997 Sep 1;57(17):3717-22. Administration of genistein to rats caused an increase in colon tumor enhancement.

1997
Divi RL and others. Antithyroid Isoflavones from the Soybean. *Biochem Pharmacol* 1997 Nov 15; 54:1087-96. This important study identifies the goitrogenic compounds in soy as the isoflavones genistein and daidzein, which were found to inhibit synthesis of thyroid hormone. Inhibition of enzymes involved in the production of thyroid hormones occurred at isoflavone levels "previously measured in plasma from humans consuming soy products." "Because inhibition of thyroid hormones synthesis can induce goiter and thyroid neoplasia in rodents, delineation of antithyroid mechanisms for soy isoflavones may be important for extrapolating goitrogenic hazards identified in chronic rodent bioassays to humans consuming soy products." The authors note that "The soybean has been implicated in diet-induced goiter by many studies."

1997
Setchell KD and others. Exposure of infants to phyto-oestrogens from soy-based infant formula. *Lancet* 1997;3530(9070):23-27. "The daily exposure of infants to isoflavones in soy infant formula is 4-11 fold higher on a body weight basis than the dose that has hormonal effects in adults consuming soy foods. Circulating concentrations of isoflavones in the seven infants fed soy-based formula were 12,000-22,000 times higher than plasma

oestradiol concentrations in early life, and may be sufficient to exert biological effects, whereas the contribution of isoflavones from breast-milk and cow-milk is negligible."

1998
Sheehan DM. Herbal medicines, phytoestrogens and toxicity:risk:benefit considerations. *Proc Soc Exp Biol Med* 1998 Mar;217(3):379-85. Knowledge of toxicity is crucial to decrease the risk:benefit ratio but herbal medicines and phytoestrogens in food are not tested as are drugs. "Important toxicities with long latencies are particularly difficult to associate with a causative agent. . . These considerations suggest that much closer study in experimental animals and human populations exposed to phytoestrogen-containing products, and particularly soy-based foods, is necessary. Among human exposures, infant soy formula exposure appears to provide the highest of all phytoestrogen doses, and this occurs during development, often the most sensitive life-stage for induction of toxicity."

1998
Strauss L and others. Dietary phytoestrogens and their Role in Hormonally Dependent Disease. *Toxicol Lett* 1998 Dec 28;102-103:349-54. Although epidemiological studies suggest that diets rich in phytoestrogens may be associated with low risk of breast and prostate cancer, there is no direct evidence for the beneficial effects of phytoestrogens in humans. It is plausible that phytoestrogens, as any exogenous hormonally active agent, might also cause adverse effects in the endocrine system.

1998
Morris SM and others. p53, mutations, and apoptosis in genistein-exposed human lymphoblastoid cells. *Mutat Res* 1998 Aug 31;405(1):41-56. In vitro administration of genistein was found to cause cellular damage and death. "Our results may be interpreted that genistein is a chromosomal mutagen. . ."

1998
Santti R and others. Phytoestrogens: Potential Endocrine Disrupters in Males. *Toxicol Ind Health* 1998 Jan-Apr;14(1-2):223-37. In doses comparable to the daily intake from soy-based feed, isoflavonoids such as genistein were estrogen agonists in the prostate of adult laboratory rodents. When given neonatally, no persistent effects were observed. In contrast, the central nervous system (CHS)-gonadal axis and the male sexual behavior of the rat appear to be sensitive to phytoestrogens during development. The changes were similar but not identical to those seen after neonatal treatment with DES, but higher doses of phytoestrogens were needed.

1998
Cheek AO and others. Environmental Signalling: a biological context for endocrine disruption. *Environ Health Perspect* 1998 Feb;106 suppl 1:5-10. The authors discuss the effects of various compounds on steroid-like signalling pathways, especially estrogen. "Based on their mechanisms of action, chemical steroid mimics could plausibly be associated with recent adverse health trends in humans and animals."

1998
Setchell KD and others. Isoflavone content of infant formulas and the metabolic fate of these early phytoestrogens in early life. *Am J Clin Nutr* 1998 Dec;68(6 Suppl):1453S-1461S. Noting the results of an earlier study which found that plasma isoflavone levels in infants fed soy-based formula were 13,000-22,000 higher than concentrations found in fed

breast milk or milk-based formula, the authors explain these high levels as due to ". . . reduced intestinal biotransformation, as evidenced by low or undetectable concentrations of equol and other metabolites, and is maintained by constant daily exposure from frequent feeding." The authors assert that these unnaturally high levels of isoflavones in the bloodstreams of soy-fed children "may have long-term health benefits for hormone-dependent diseases."

1998
McMichael-Phillips DF and others. Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. *Am J Clin Nutr* 1998 Dec;68(6 Suppl):1431S-1435S. Forty-eight women with benign or malignant breast disease were randomly assigned a normal diet either alone or with a 60 gram soy supplement containing 45 mg isoflavones, taken for 14 days. The proliferation rate of breast lobular epithelium significantly increased after just 14 days of soy supplementation when both the day of menstrual cycle and age of patient were accounted for. Thus short-term dietary soy containing isoflavone levels found in modern soy foods stimulates breast proliferation.

1998
Strauss and others. Genistein exerts estrogen-like effects in make mouse reproductive tract. *Mol Cell Endocrinol* 1998 Sept 25;144(1-2):83-93. Genistein was found to have estrogenic effects in adult male mice, at doses comparable to those present in soy-based human diets. In neonatal animals, considerably higher doses are required to show estrogen-like activity."

1998
Irvine CH and others. Daily intake and urinary excretion of genistein and daidzein by infants fed soy- or dairy-based infant formulas. *Am J Clin Nutr* 1998 Dec;68(6 Suppl):1462S-1465S. A report on the work of Setchell (above), noting that the effects of high levels of estrogen in infant formula are likely to be detrimental rather than beneficial.

1999
Casanova M and others. Developmental effects of dietary phytoestrogens in Sprague-Dawley rats and interactions of genistein and daidzein with rat estrogen receptors alpha and beta in vitro. *Toxicol Sci* 1999 Oct;51(2):236-44. Effects of dietary genistein included a decreased rate of body-weight gain, a markedly increased (2.3 fold) uterine/body weight and a significant acceleration of puberty among females.

1999
Fisher JS and others. Effect of neonatal exposure to estrogenic compounds on development of the excurrent ducts of the rat testis through puberty to adulthood. *Environ Health Perspect* 1999 May;107(5):397-405. Administration of genistein to rats caused minor but significant changes in rat testes. "This study suggests that structural and functional. . . development of the excurrent ducts is susceptible to impairment by neonatal estrogen exposure, probably as a consequence of direct effects. The magnitude and duration of adverse changes induced by treatment with a range of estrogenic compounds was broadly comparable to their estrogenic potencies reported from in vitro assays."

1999
Pan Y and others. Effect of estradiol and soy phytoestrogens on choline acetyltransferase and nerve growth factor mRNAs in the frontal cortex and hippocampus of female rats. *Proc Soc Exp Biol Med* 1999 Jun;221(2):118-25. "Our data suggest that soy phytoestrogens may

function as estrogen agonists in regulating CHAT and NDF mRNBAs in the brain of female rats."

1999
Kulling SE and others. The phytoestrogens coumoestrol and genistein induce structural chromosomal aberrations in cultured human peripheral blood lymphocytes. *Arch Toxicol* 1999 Feb;73(1):50-4. Exposure of blood lymphocytes to low levels of genistein in vitro caused chromosomal aberrations including chromatid breaks, gaps and interchanges. Exposure to daidzein did not cause aberrations, even at high levels. The results suggest that ". . . some but not all phytoestrogens have the potential for genetic toxicity."

1999
Abe T. Infantile leukemia and soybeans--a hypothesis. *Leukemia* 1999 Mar;13(3)317-20. Genistein from soybeans contributes to DNA strand breaks and may be "largely responsible" for infantile acute leukemia.

1999
Hilakavi-Clarke and others Exposure to genisten during pregnancy increases carcinogen-induced mammary tumorigenesis in female rat offspring. *Oncol Rep* 1999 Sep-Oct;6(5):1089-95. Dietary genistein was found to enhance the growth of mammary gland tumors in mice. The results suggest ". . . that a maternal exposure to subcutaneous administration of genistein can increase mammary tumorigenesis in the offspring, mimicking the effects of in utero estrogen exposures."

1999
Nagata C and others. Hot flushes and other menopausal symptoms in relation to soy product intake in Japanese women. *Climacteric* 1999 Mar;2(1):6-12. Intake of fermented soy products was found to reduce the severity of hot flashes in Japanese women, but not total soy intake (from unfermented soy products such as are found in western diets). This study is included because it contradicts assertions that Japanese women do not suffer from hot flashes.

2000
Gee JM and others. Increased induction of aberrant crypt foci by 1,2-dimethylhydrazine in rats fed diets containing purified genistein or genistein-rich soya protein. *Carcinogenesis* 2000 Dec;21(12):2255-9. Genistein promotes induction of aberrant crypt foci by an as yet unidentified mechanism when fed immediately before treatment with 1,2-dimethylhydrazine.

2000
Cassanova N and others. Comparative effects of neonatal exposure of male rats to potentand weak (environmental) estrogens on spermatogenesis at puberty and the relationship to adult testis size and fertility: evidence for stimulatory effects of low estrogen levels. *Endocrinology* 2000 Oct;141(10):3898-907. Administration of genistein to rats significantly retarded most measures of pubertal spermatogenesis. Animals fed a soy-free diet had significantly larger testes than controls fed a soy-containing diet. "It is concluded that. . . the presence or absence of soy or genistein in the diet has significant short-term (pubertal spermatogenesis) and long-term (body weight, testis size, FSH levels and possibly mating) effects on males."

2000
Watanabe S and others. Effects of isoflavone supplement on healthy women. *Biofactors* 2000;12(1-4):233-41. After one month of taking 20 mg or 40 mg isoflavones daily, 60% of the young women had prolonged menstruation, 20% had shortened menstruation, 17% remained unchanged and 3% became irregular. Other hormonal changes "suggest that isoflavones influence not only estrogen receptor-related functions but the hypothalamo-hypophysis-gonadal axis."

2000
Yang J and others. Influence of perinatal genistein exposure on the development of MNU-induced mammary carcinoma in female Sprague-Dawley rats. *Cancer Lett* 2000 Feb 28;149(1-2):171-9. ". . . perinatal genistein is an endocrine disrupter and increases the multiplicity of MNU-induced mammary carcinoma in rats."

2000
Salti GI and others. Genistein induces apoptosis and topoisomerase II-mediated DNA breakage in colon cancer cells. *Eur J Cancer* 2000 Apr;36(6):796-802. DNA breakage in colon cancer cells occurred within 1 hour of treatment with genistein.

2000
Lephard ED and others. Phytoestrogens decrease brain calcium-binding proteins but do not alter hypothalamic androgen metabolizing enzymes in adult male rats. *Brain Res* 2000 Mar 17;859(1):123-31. Animals fed diets containing phytoestrogens for 5 weeks had elevated levels of phytoestrogens in the brain and a decrease of brain calcium-binding proteins. Calcium-binding proteins are associated with protection against neurodegenerative diseases.

2000
Strick R and others. Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. *Proc Natl Acad Sci USA* 2000 Apr 25;97(9):4790-5. Researchers found that flavonoids, especially genistein, can cross the placenta and induce cell changes that lead to infant leukemia.

2000
Chang HS and Doerge DR. Dietary genistein inactivates rat thyroid peroxidase in vivo without an apparent hypothyroid effect. *Toxicol Appl Pharmacol* 2000 Nov 1;168(3):244-52. The activity of thyroid peroxidase activity in soy-fed rats was reduced by up to 80% compared to those on a soy-free diet. As thyroid hormone levels and thyroid weights were no different between treated and untreated groups, the researchers concluded that "the remaining enzymatic activity is sufficient to maintain thyroid homeostasis in the absence of additional perturbations." However, it is difficult or impossible to measure some of the more subtle manifestations of hypothyroidism in rats.

2000
Gee JM and others. Increased induction of aberrant crypt foci by 1,2-dimethylhydrazine in rats fed diet containing purified genistein or genistein-rich soya protein. *Carcinogenesis* 2000;21:2255-2259. Rats fed the isoflavone genistein exhibited pathological changes in the colon.

2000
Ikeda T and others. Dramatic synergism between excess soybean intake and iodine

deficiency on the development of rat thyroid hyperplasia. *Carcinogenesis* 2000 Apr;21(4):707-13. Excess soybean intake with iodine deficiency caused abnormal growth of the thyroid gland.

2000
Nagata C and others. Inverse association of soy product intake with serum androgen and estrogen concentrations in Japanese men. *Nutr Cancer* 2000;36(1):14-8. Researchers found lower testosterone levels and higher estrogen levels in Japanese men who consumed higher levels of soy foods.

2000
Chang HC and others. Mass Spectrometric determination of Genistein tissue distribution in diet-exposed Sprague-Dawley rats. *J Nutr* 2000 Aug;130(8):1963-70. Genistein administered to mice via maternal milk or fortified feed showed dose-dependent increases in total genistein concentration in the brain, liver, mammary, ovary, prostate, testis, thyroid and uterus.

2000
Flynn KM and others. Effects of genistein exposure on sexually dimorphic behaviors in rats. *Toxicol Sci* 2000 Jun;55(2):311-9. Noting that genistein "has adverse effects on animal reproduction," the researchers administered genistein to pregnant rats and to their offspring during growth. Results indicated significantly decreased body weight in genistein-fed rats compared to controls. The results indicate that developmental genistein treatment, at levels that decrease maternal and offspring body weight, causes subtle alternations in some sexually dimorphic behaviors.

2000
Habito RC and others. Effects of replacing meat with soyabean in the diet on sex hormone concentrations in healthy adult males. *Br J Nutr* 2000 Oct;84(4):557-63. Men consuming tofu instead of meat for 4 weeks had lower testosterone-oestradiol ratios as well as changes in other hormone levels. "Thus, replacement of meat protein with soyabean protein, as tofu, may have a minor effect on biologically-active sex hormones which could influence prostate cancer risk."

2000
Pino AM and others. Dietary isoflavones affect sex hormone-binding globulin levels in postmenopausal women. *J Clin Endocrinol Metab* 2000;85:2797-2800. Soy consumption increased sex hormone-binding globulin (SHGB) levels in postmenopausal women, which is evidence of endocrine disruption.

2000
Quella SK and others. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. *J Clin Oncol* 2000 Mar;18(5):1068-1074. Soy did not relieve hot flashes in breast cancer survivors.

2000
Kotsopoulos D and others. The effects of soy protein containing phytoestrogens on menopausal symptoms in postmenopausal women. *Climacteric* 2000 Sep;3(3):153-4. A study carried out at Monash University, Clayton, Australia found that three months of soy supplements providing 188 mg of isoflavones daily did not improve menopausal complaints in 94 older postmenopausal women compared with those taking a placebo.

2000
Messina M. soyfoods and soybean phyto-oestrogens (isoflavones) as possible alternatives to hormone replacement therapy. *Eur J Cancer*. 2000 Sep ;36 Suppl 4 :271-2. Soy apologist Mark Messina argues that soy is better than hormone replacement therapy because soy "seems unlikely to increase risk because it has no progestin activity." He notes that there is no evidence to suggest that soy will increase the incidence of clots or stroke but "only limited data are available in this area." Ditto for heart disease, osteoporosis and colon cancer--soy may help but the evidence is scanty. ". . . [T]he evidence warrants recommendations that menopausal women include soy in their diets," Messina does not mention the growing number of studies, including the one above, showing that soy offers no benefit at all for menopausal problems. Symptoms typically improve on their own. Why not just take the placebo--at least it won't depress thyroid function or upset the delicate chemistry of breast tissue.

2001
Badger TM and others. Developmental effects and health aspects of soy protein isolate, casein and whey in male and female rats. *Int J Toxicol* 2001 May-Jun;20(3);165-74. Feeding of soy protein isolate was found to accelerate puberty in female rats. Female rats also had reduced serum 17beta-estradiol concentrations.

2001
Doerge DR and others. Placental transfer of the soy isoflavone genistein following dietary and gavage administration to Sprague Dawley rats. *Reprod Toxicol* 2001 Mar-Apr;15(2):105-10. Genistein was found to cross the rat placenta and reach the fetal brain in doses similar to those observed in humans.

2001
Newbold RR and others. Uterine adenocarcinoma in mice treated neonatally with genistein. *Cancer Res* 2001 Jun 1;61(11):4325-8. Genistein in soy was found to be more carcinogenic than DES, especially during "critical periods of differentiation.. . . the use of soy-based infant formulas in the absence of medical necessity and the marketing of soy products designed to appeal to children should be closely examined."

2001
Declos KB and others. Effects of dietary genistein exposure during development on male and female DC (Sprague-Dawley) rats. *Reprod Toxicol* 2001 Nov;15(6):647-63. Genistein was administered to rats at various concentrations starting on gestation day 7 and continuing throughout pregnancy, lactation and growth of the pups to day 50. The genistein-fed rats showed a number of variances from the norm: lower weight in both sexes; decreased prostate weight in males; higher pituitary gland to body weight ratios in both sexes; hyperplasia of the mammary glands, abnormal ovarian antral follicles and abnormal cellular maturation in the vagina in females; aberrant or delayed spermatogenesis and deficit sperm in males; and an increase in the incidence and/or severity of renal tubal

mineralization in both sexes, even at low doses. "Dietary genistein thus produced effects in multiple estrogen-sensitive tissues in males and females that are generally consistent with its estrogenic activity. These effects occurred within exposure ranges achievable in humans."

2001
Thigpen JE and others. Effects of the dietary phytoestrogens daidzein and genistein on the incidence of vulvar carcinomas in 129/J mice. *Cancer Detect Prev* 2001;25(6):527-32. Within one month, the incidence of vulvar carcinomas in mice fed a modified soy protein diet was significantly increased over those of mice fed control diets. Within three months, the incidence of vulvar carcinomas in mice fed the soy protein diet was significantly increased over those of mice fed other control diets. "We concluded that dietary levels of daidzein and genistein were associated with an increase in the incidence of vulvar carcinomas in mice. . ."

2001
de Lemos ML. Effects of soy phytoestrogens genistein and daidzein on breast cancer growth. *Ann Pharmacother* 2001 Sep;35(9):118-21. "Genistein and daidzein may stimulate existing breast tumor growth and antagonize the effects of tamoxifen. Women with current or past breast cancer should be aware of the risks of potential tumor growth when taking soy products."

2001
Ju YH and others. Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. *J Nutr* 2001 Nov;131(11):2957-62. Genistein stimulated breast tumor growth and cell proliferation in mice in a dose-responsive manner.

2001
Zhang QH and others. Inhibitory effect of genistein on the proliferation of the anterior pituitary cells of rats. *Sheng Li Xue Bao* 2001 Feb;53(1):51-4. Genistein inhibits proliferation and causes apoptosis of pituitary cells by inhibiting tyrosine kinase activity.

2001
Nagao T and others. Reproductive effects in male and female rats of neonatal exposure to genistein. *Reprod Toxicol* 2001 Jul-Aug;15(4):399-411. Feeding of genistein to newborn rats resulted in lower body weight in male and female rats, estrous cycle irregularities and lowered fertility in female rats. Neonatal exposure to genistein caused dysfunction of postpubertal reproduction performance as well as abnormal development of gonads in female but not in male rats.

2001
Slikker W Jr and others. Gender-based differences in rats after chronic dietary exposure to genistein. *Int J Toxicol* 2001 May-Jun;20(3):175-9. Dose-related alternations of the volume of the sexually dimorphic nucleus of the medial preoptic area were observed in genistein-exposed male rats but not females.

2001
den Tonkelaar I and others. Urinary phytoestrogens and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2001 Mar;10(3):223-8. "We were not able to detect the

previously reported protective effects of genistein and enterolactone on breast cancer risk in our postmenopausal population of Dutch women."

2001
Bennetau-Pelissero C and others. Effect of genistein-enriched diets on the endocrine process of gametogenesis and on reproduction efficiency of the rainbow trout Oncorhynchus mykiss. *Gen Comp Endocrinol* 2001 Feb;121(2):173-87. Genistein caused a decrease in testosterone levels in rainbow trout. Testicular development was accelerated in genistein-fed fish and sperm motility and concentration were decreased in a dose-dependent manner at spawning.

2001
Patisual HB and others. Soy isoflavone supplements antagonize reproductive behavior and estrogen receptor alpha- and beta-dependent gene expression in the brain. *Endocrinology* 2001 Jul;142(7):2946-52. Soy isoflavones interfere with estrogen receptors in the adult female rat brain resulting in a significant decrease in receptive behavior in estrogen- and progesterone-primed females. "The observed disruption of sexual receptivity by the isoflavone supplement is probably due to antiestrogenic effects observed in the brain."

2001
Whitten PL and Patisaul HB. Cross-species and interassay comparisons of phytoestrogen actions. *Environ Health Perspect* 2001 Mar;109 Suppl 1:5-20. "In vivo data show that phytoestrogens have a wide range of biologic effects at doses and plasma concentrations seen with normal human diets. Significant in vivo responses have been observed in animal and human tests for bone, breast, ovary, pituitary, vasculature, prostate and serum lipids. . . . Steroidogenesis and the hypothalamic-pituitary-gonadal axis appear to be important loci of phytoestrogen actions, but these inferences must be tentative because good dose-response data are not available for many end points."

2001
Shibayama T and others. Neonatal exposure to genistein reduces expression of estrogen receptor alpha and androgen receptor in testes of adult mice. *Endocr J* 2001 Dec;48(6):655-63. "Our results exhibited that the disruption of gene expression continued for long term such as 3 months after administration of genistein, even if no effect was found at conventional reproductive-toxicological levels. We have shown that neonatal administration of weak estrogenic compound (genistein) affects male reproductive organs at molecular levels in adulthood."

2001
Lephart ED and others. Dietary soy phytoestrogen effects on brain structure and aromatase in Long-Evans rats. *Neuroreport* 2001 Nov 16;12(16):3451-5. Dietary phytoestrogens significantly decrease body and prostate weights and during adulthood significantly change the structure of the sexually dimorphic brain region in male but not in female rats.

2001
Allred CD and others. Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. *Cancer Res* 2001 Jul 1;61(13):5045-50. Soy protein isolates containing increasing concentrations of genistein stimulate the growth of estrogen-dependent breast cancer cells in vivo in a dose-dependent manner.

2001
Allred CD and others. Dietary genistin stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein. *Carcinogenesis* 2001 Oct;22(10):1667-73. Genistin, the glycoside form of genistein, is converted to genistein by human saliva. The glycoside genistin, like the aglycone genistein, can stimulate estrogen-dependent breast cancer cell growth in vivo. Removal of genistin or genistein from the diet caused tumors to regress.

2001
St. Germain A and others. Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment. *Menopause* 2001 Jan-Feb;8(1):17-26. Investigators at the Department of Food Science and Human Nutrition at Iowa State University examined changes in menopausal symptoms in response to 24 weeks of isoflavone-rich diets, comparing women receiving about 80 of mg isoflavones per day with a group receiving 4 mg per day and a group receiving none. They found no treatment effect on frequency, duration or severity of hot flashes or night sweats. All groups reported a decline in overall symptoms, indicating either a placebo effect or simply an improvement in symptoms during the study.

2002
Jefferson W and others. Assessing estrogenic activity of phytochemicals using transcriptional activation and immature mouse uterotrophic responses. *J Chromatogr B Analyt Technol Biomed Life Sci* 2002 Sep 25;777(1-2):179. Genistein caused an increase in uterine weight and several other indications of estrogenicity.

2002
Kulling S and others. Oxidative metabolism and genotoxic potential of major isoflavone phytoestrogens. *J Chromatogr B Analyt Technol Biomed Life Sci* 2002 Sep 25;777(1-2):211. The study describes the potential genetic toxicity of the breakdown products of soy isoflavones.

2002
Doerge D and Chang H. Inactivation of thyroid peroxidase by soy isoflavones, in vitro and in vivo. *J Chromatogr B Analyt Technol Biomed Life Sci* 2002 Sep 25;777(1-2):269. The paper reviews the evidence in humans and animals for anti-thyroid effects of soy and its principal isoflavones, genistein and daidzein. Genistein interferes with estrogen receptors in rat prostate glands which ". . . may have implications for reproductive toxicity and carcinogenesis that warrant further investigation."

2002
Whitehead SA and others. Acute and chronic effects of genistein, tyrphostin and lavendustin A on steroid synthesis in luteinized human granulosa cells. *Hum Reprod* 2002 Mar;17(3):589-94. Genistein directly inhibits steroid-production enzymes.

2002
Foster WG and others. Detection of phytoestrogens in samples of second trimester humanamniotic fluid. *Toxicol Lett* 2002 Mar 28;129(3):199-205. The study describes a method for measuring phytoestrogens daidzein and genistein in amniotic fluid. Such tests

are needed, the authors assert, because "There is widespread concern that fetal exposure to hormonally active chemicals may adversely affect development of the reproductive tract."

2002
Klein SL and others. Early exposure to genistein exerts long-lasting effects on the endocrine and immune systems in rats. *Mol Med* 2002 Nov;8(11):742-9. Pregnant female rats were exposed to no, low (5 mg/kg diet) or high (300 mg/kg diet) genistein diets throughout gestation and lactation. At weaning, male offspring exposed to genistein perinatally were either switched to the genistein-free diet or remained on the genistein-dosed diets. At 70 days of age, immune organ masses, lymphocyte subpopulations, cytokine concentrations and testosterone concentrations were assessed in male offspring. Relative thymus masses were greater among males expose d to the high genistein diet than among males exposed to no genistein and certain markers of immune system function were also lower. Testosterone concentrations were lower among genistein-exposed than genistein-free males. These data illustrate that exposure to genistein during pregnancy and lactation exerts long-lasting effects on the endocrine and immune systems in adulthood. Whether exposure to phytoestrogens during early development affects responses to infectious or autoimmune diseases, as well as cancers, later in life requires investigation.

2002
Silva E and others. Something from "nothing"--eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. *Environ Sci Technol* 2002 Apr;36(8):1751-6. Xenoestrogens including genistein were tested in combinations. The results were additive, producing significant effects when combined at low concentrations. "Our results highlight the limitations of the traditional focus on the effects of single agents. Hazard assessments that ignore the possibility of joint action of estrogenic chemicals will almost certainly lead to significant underestimations of risk."

2002
Doerge DR and DM Sheehan. Goitrogenic and estrogenic activity of soy isoflavones. *Environ Health Perspect* 2002 Jun;110 suppl 3:349-53. "Soy is known to produce estrogenic isoflavones. Here, we briefly review the evidence for binding of isoflavones to the estrogen receptor, in vivo estrogenicity and developmental toxicity, and estrogen developmental carcinogenesis in rats. Genistein, the major soy isoflavone, also has a frank estrogenic effect in women. We then focus on evidence from animal and human studies suggesting a link between soy consumption and goiter, an activity independent of estrogenicity. Iodine deficiency greatly increases soy antithyroid effects, whereas iodine supplementation is protective. . . . Although safety testing of natural products, including soy products, is not required, the possibility that widely consumed soy products may cause harm in the human population via either or both estrogenic and goitrogenic activities is of concern."

2002
Ju YH and others. Dietary genistein negates the inhibitory effect of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. *Cancer Res* 2002 May 1;62(9):2474-7. Dietary genistein negated or overwhelmed the inhibitor effect of tamoxifen on tumor growth in ovariectomized and athymic mice. "Therefore, caution is warranted for postmenopausal women consuming dietary genistein while on TAM therapy for E-responsive breast cancer."

2002
Guo TL and others. Genistein modulates splenic natural killer cell activity, antibody-forming cell response and phenotypic marker expression in F(0) and F(1) generations of Sprague-Dawley rats. *Toxicol Appl Pharmacol* 2002 Jun 15;181(3):219-27. Genistein caused a decrease in the percentage of helper T cells and an increase in the relative weights of spleen and thymus in rats.

2002
Patisaul HB and others. Genistein affects ER beta- but not ER alpha-dependent gene expression in the hypothalamus. *Endocrinology* 2002 Jun;143(6):2189-97. Genistein at a dietary concentration of 100 or 500 ppm had no effect on lordosis behavior in rats. However, at 500 ppm genistein had differential activity through ER alpha and ER beta in the hypothalamus.

2002
Whitten PL and others. Neurobehavioral actions of coumestrol and related isoflavonoids in rodents. *Neurotoxicol Teratol* 2002 Jan-Feb;24(1):47-54. Coumestrol and related isoflavones induced neurobehavioral actions in rodents that were antiestrogenic, either antagonizing or producing an action in opposition to that of estradiol. "This work demonstrates that even small, physiologically relevant exposure levels can alter estrogen-dependent gene expression in the brain and complex behavior."

2002
Nicholls J and others. Effects of soy consumption on gonadotropin secretion and acute pituitary responses to gonadotropin-releasing hormone in women. *J Nutr* 2002 Apr;132(4):708-14. Twelve women consumed 60 mg isoflavones daily for 10-14 days. A residual postmenopausal effects was seen in postmenopausal subjects. "In one premenopausal woman, enhanced LH secretion was observed after soy treatment, suggesting there may be sub-populations of women who are highly sensitive to isoflavones."

2002
Kumar NB and others. The specific role of isoflavones on estrogen metabolism in premenopausal women. *Cancer* 2002 Feb 15;94(4):1166-74. Sixty eight women consuming 40 mg soy isoflavones daily for 12 weeks had changes in steroid hormones and increased cycle length.

2002
You L and others. Combined effects of dietary phytoestrogen and synthetic endocrine-active compounds on reproductive development in Sprague-Dawley rats: genistein and methoxychlor. *Toxicol Sci* 2002 Mar;66(1):91-104. "Data from this study indicate that phytoestrogens are capable of altering the toxicological behaviors of other EACs, and the interactions of these compounds may involve complexities that are difficult to predict based on their in vitro steroid receptor reactivities."

2002
Degen GH and others. Transplacental transfer of the phytoestrogen daidzein in DA/Han rats. *Arch Toxicol* 2002 Feb;76(1):23-9. The research found indications of a rapid transfer of daidzen from the mother to the fetus, but also that efficient extraction of daidzein from the maternal blood occurs. "Since dietary phytoestrogens account for a significant proportion of

human exposure to potential endocrine modulators, and since the placenta does not represent a barrier to daidzein or related estrogenic isoflavones, the consequences of these exposures early in life should be examined and monitored carefully."

2002
Sharpe RM and others. Infant feeding with soy formula milk: effects on the testis and on blood testosterone levels in marmoset monkeys during the period of neonatal testicular activity. *Hum Reprod* 2002 Jul;17(7):1692-703. Infant male marmoset monkeys were fed either soy-based or milk-based formula. The neonatal testosterone rise was suppressed in the soy-fed monkeys. Levels of isoflavone in the monkey diets were 40-87% of that reported in 4-month human infants fed a 100% soy-based formula diet. "It is therefore considered likely that similar, or larger, effects to those shown here in marmosets may occur in human male infants fed with SFM [soy formula milk]."

2002
Chiang, CE and others. Genistein Inhibits the Inward Rectifying Potassium Current in Guinea Pig Ventricular Myocytes. *J Biomed Sci* 2002;9:321-326. Dietary isoflavones genistein dose-dependently and reversibly inhibit the inward rectifying K+ (potassium) current in guinea pigs ventricular myocytes, suggesting the potential for soy isoflavones to cause heart arrhythmias.

2002
Yellaya S and others. The phytoestrogen genistein induces thymic and immune changes: a human health concern? *Proc Natl Acad Sci USA* 2002 May 28;99(11):7616-21. Genistein injections in ovariectomized adult mice produce dose-responsive decreased in thymic weight of up to 80%. Genistein decreased thymocyte numbers up to 86% and doubled apoptosis. There was a corresponding reduction in splenic cells. The dose that caused significant thymic and immune changes in mice was comparable to those reported in soy-fed human infants. "These results raise the possibility that serum genistein concentrations found in soy-fed infants may be capable of producing thymic and immune abnormalities, as suggested by previous reports of immune impairments in soy-fed infants."

2002
Lephard ED and others. Neurobehavioral effects of dietary soy phytoestrogens. *Neurotoxicol Teratol* 2002 Jan-Feb;24(1):5-16. Male mice fed diets rich in phytoestrogens had lower levels of maze performance than male mice fed diets free of phytoestrogens. (Opposite results were observed in female mice.) The results indicate that consumption of dietary phytoestrogens resulting in very high plasma isoflavone levels (in many cases over a relatively short interval of consumption in adulthood) can significantly alter sexually dimorphic brain regions, anxiety, learning and memory.

2002
Newbold R and others. Increased uterine cancer seen in mice injected with genistein, a soy estrogen, as newborns. *Cancer Research* 2002 Jun 1;61(11):4325-8. Infant mice given genistein developed cancer of the uterus later in life. "The data suggest that genistein is carcinogenic if exposure occurs during critical periods in a young animal's development."

2002
Balk JL and others. A pilot study of the effects of phytoestrogen supplementation on postmenopausal endometrium. *J Soc Gynecol Investig* 2002 Jul-Aug;9(4)238-42. This was a

double-blinded, randomized, placebo-controlled trial comparing the effects of 6 months of dietary phytoestrogen supplementation versus placebo in postmenopusal women. "Phytoestrogens did not cause stimulation of the endometrium. Insomnia was more frequent over the 6-month study in the soy group, whereas hot flushes, night sweats and vaginal dryness improved from baseline in the placebo group but not in the soy group."

2003
Gardner-Thorpe D and others. Dietary supplements of soya flour lower serum testosterone concentrations and improve markers of oxidative stess in men. *Eur J Clin Nutr* 2003 Jan;57(1):100-6. In a study carried out at University Hospital of Wales, male volunteers ate three scones per day in addition to their normal diet for a period of six weeks. The scones were made either with wheat flour or soy flour providing 120 mg per day of isoflavones (about the amount contained in 3 cups of soy milk). Researchers noted "significant improvements in two of the three markers of oxidative stress" and concluded that "these findings provide a putative mechanism by which soya supplements could protect against prostatic disease and atherosclerosis. However, testosterone levels fell in the volunteers eating the soy but researchers did not stress this alarming finding in their conclusion

2001
Bell DS and others. Use of soy protein supplement and resultant need for increased dose of levothyroxine. *Endocr Pract* 2001 May-Jun;7(3):193-4). The University of Alabama at Birmingham reports a case in which consumption of a soy protein dietary supplement decreased the absorption of thyroxine. The patient had undergone thyroid surgery and needed to take thyroid hormone. Higher oral doses of thyroid hormone were needed when she consumed soy--she presumably used iodized salt so iodine intake did not prevent the goitrogenic effects of soy. Although soy has been known to suppress thyroid function for over 60 years, and although scientists have identified the goitrogenic component of soy as the so-called beneficial isoflavones, the industry insists that soy depresses thyroid function only in the absence of iodine.

2002
Jefferson WN and others. Neonatal exposure to genistein induces estrogen receptor (ER)alpha expressionand multioocyte follicles in the maturing mouse ovary: evidence for Erbeta-mediated and nonestrogenic actions. *Biol Reprod* 2002 Oct;67(4):1285-96. Scientists at the National Institute of Environmental Health Sciences in North Carolina treated newly born mice with the soy phytoestrogen genistein for the first five days after birth. They found that significant alterations occurred in the ovaries. Their conclusion: "Given that human infants are exposed to high levels of genistein in soy-based foods, this study indicates that the effects of such exposure on the developing reproductive tract warrant further investigation."

2003
Wisniewski AB and others. Exposure to genistein during gestation and lactation demasculinizes the reproductive system in rats. *Journal of Urology*, April 2003 169:1582-1586. In order to determine the effects of exposure to phytoestrogens, researchers at the Johns Hopkins Children's Center and the Johns Hopkins Bloomberg School of Public Health randomly assigned pregnant female rats to diets containing none, low and high levels of genistein--the major type of phytoestrogen in soy. The male offspring were thus exposed to genistein indirectly through maternal consumption during pregnancy and lactation. Female rats on the low-genistein diet received between 0.1 and 1.0 mg genistein per day while

those on the high-genistein diet received between 6.4 and 23.6 mg genistein per day--somewhat equivalent to the exposure of mothers consuming small amounts and large amounts of soy. Male offspring of mothers on the high-genistein diet exhibited reproductive abnormalities and rats exposed to both the low- and high-genistein diets had shorter testes length, larger prostate mass and lower testosterone concentrations. The researchers also looked at adult sexual behavior of male offspring. Those exposed to both low and high doses of genistein were less likely to ejaculate after mounting female rats. Most interesting was the fact that males exposed to the low dose were less likely to mount and begin the process of intercourse than males whose mothers received the free or high-genistein diets. Thus, although adult sperm counts were not affected by exposure to genistein, the male rats exhibited "persistent demasculinization of the male reproductive system." Ejaculatory behavior was significantly reduced by exposure to genistein. Most significant was the observation that "the low dose led to alterations in male development to a greater degree than the high dose." This is consistent with other studies reporting "an inverted U-shaped dose response" in males exposed to low and high doses of estrogenic substances. What this means is that pregnant and nursing mothers should avoid all soy as even a low-dose exposure to genistein caused subtle but significant changes in sexual behavior in male offspring.

2003
Penotti M and others. Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertil Steril* 2003 May;79(5):1112-1117). In a study carried out by the University of Milan came to the same conclusion, patients were administered 72 mg per day of soy-derived isoflavones or placebo under double-blind conditions. There was no advantage to the group receiving isoflavones. Both groups recorded a 40 percent reduction in the number of hot flashes.

2003
Nikander E and others. A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstetrics and Gynecology* 2003;101:1213-1220And, finally, a study carried out in Helsinki University Central Hospital found no difference between phytoestrogens and a placebo for treating menopausal symptoms in breast cancer survivors.

2003
Hartley DC and others. The soya isoflavone content of rat diet can increase anxiety and stress hormone release in the male rat. *Psychopharmacology (Berl)* 2003 Apr ;167(1) :46-53. This report begins with the following statement: "Isoflavones form one of the main classes of phytoestrogens and have been found to exert both oestrogenic and anti-oestrogenic effects on the central nervous system. The effects have not been limited to reproductive behaviour, but include effects on learning and anxiety and actions on the hypothalamo-pituitary axis." Noting that most rat chow contains soy, investigators compared the behavior of rats given isoflavones in their diets with those on an isoflavone-free diet. Rats fed isoflavones spent significantly less time in active social interaction and had significantly elevated stress-induced corticosterone concentrations. The conclusion: "Major changes in behavioural measures of anxiety and in stress hormones can result from the soya isoflavone content of rat diet. These changes are as striking as those seen following drug administration and could form an important source of variation between laboratories."

STUDIES SHOWING ADVERSE EFFECTS OF DIETARY SOY, 1971-2003

1971
Wallace, GM. Studies on the Processing and Properties of Soymilk. *J Sci Food Agri* 1971 Oct;22:526-535. In order to neutralize the protease inhibitors (enzymes that inhibit the digestion of protein) in soy, it must be heated to very high temperatures under pressure and for considerable time. This process unfortunately denatures the overall protein content of soy, rendering it largely ineffective.

1974
Joseph, JR. Biological and physiological Factors in Soybeans. *JOACS*, 1974 Jan;51:161A-170A. In feeding experiments, use of soy protein isolate (SPI) increased requirements for vitamins E, K, D and B12 and created deficiency symptoms of calcium, magnesium, manganese, molybdenum, copper, iron and zinc.

1975
Nutrition during Pregnancy and Lactation. California Department of Health, 1975. Soy is listed as a minor source of protein in Japanese and Chinese diets. Major sources of protein listed were meat including organ meats, poultry, fish and eggs.

1976
Searle CE, ed, *Chemical Carcinogens*, ACS Monograph 173, American Chemical Society, Washington, DC, 1976. Asians throughout the world have high rates of thyroid cancer.

1977
Chang KC, ed, *Food in Chinese Culture: Anthropological and Historical Perspectives*, New Haven, 1977. This survey found that soy foods accounted for only 1.5 percent of calories in the Chinese diet, compared with 65 percent of calories from pork.

1978
FDA ref 72/104, Report FDABF GRAS - 258. In 1972, the Nixon administration directed a reexamination of substances believed to be GRAS in the light of any scientific information then available. This reexamination included casein protein which became codified as GRAS in 1978. In 1974, the FDA obtained a literature review of soy protein because, as soy protein had not been used in food until 1959 and was not even in common use in the early 1970s, it was not eligible to have its GRAS status grandfathered under the provisions of the Food, Drug and Cosmetic Act.

1979
Evaluation of the Health Aspects of Soy Protein Isolates as Food Ingredients. Prepared for FDA by Life Sciences Research Office, *Federation of American Societies for Experimental Biology*, 9650 Rockville Pike, Bethesda, MD 20014, Contract No, FDA 223-75-2004, 1979. In this document, the FDA expresses concern about nitrites and lysinoalanine in processed soy. Even at low levels of consumption--averaging one-third of a gram per day at the time--the presence of these carcinogens was considered too great a threat to public health to allow GRAS status. Soy protein did have approval for use as a binder in cardboard boxes and this approval was allowed to continue because researchers considered that migration of nitrites from the box into the food contents would be too small to constitute a cancer risk. FDA officials called for safety specifications and monitoring procedures before granting of GRAS

status for food. These were never performed. To this day, use of soy protein is codified as GRAS only for limited industrial use as a cardboard binder.

1979
Torum, B. Nutritional Quality of Soybean Protein Isolates: Studies in Children of Preschool Age. *Soy Protein and Human Nutrition*, Harold L Wilcke and others, eds, Academic Press, New York, 1979. A group of Central American children suffering from malnutrition was first stabilized and brought into better health by feeding them native foods, including meat and dairy products. Then for a two-week period these traditional foods were replaced by a drink made of soy protein isolate and sugar. All nitrogen taken in and all nitrogen excreted were measured. The researchers found that the children retained nitrogen and that their growth was "adequate," so the experiment was declared a success. However, the researchers noted that the children vomited "occasionally," usually after finishing a meal; over half suffered from periods of moderate diarrhea; some had upper respiratory infections; and others suffered from rash and fever. It should be noted that the researchers did not dare to use soy products to help children recover from malnutrition, and were obliged to supplement the soy?sugar mixture with nutrients largely absent in soy products, notably vitamins A, D, B12, iron, iodine and zinc.

1981
Casey CE and others . Availability of zinc: loading tests with human milk, cow's milk, and infant formulas. *Pediatrics* 1981;68(3):394-6. Female subjects consumed 25 mg of zinc with milk or formula, the amount of which was calculated to provide 5 gm of protein, after an eight-hour fast. Blood samples were taken prior to (base line) and at 30-minute intervals for three hours after consumption of zinc. The plasma response with human milk was significantly greater than with cow's milk and all the formulas. The response with cow's milk and a cow's milk-based formula was one third that with human milk; responses with a soy-based and two casein hydrolysate-based formulas were even lower.

1981
Lebenthal E and others. The development of pancreatic function in premature infants after milk-based and soy-based formulas. *Pediatr Res* 1981 Sep;15(9):1240-1244. Soy formula fed to premature babies caused in increase in digestive enzymes compared to milk-fed babies, indicating low digestibility of soy formula.

1982
Murphy PA. Phytoestrogen Content of Processed Soybean Foods. *Food Technology*. 1982:50-54. One hundred grams of soy protein, the maximum suggested cholesterol-lowering dose in the FDA-sanctioned health claim, can contain almost 600 mg of isoflavones.

1983
Wenk GL and Stemmer KL. Suboptimal dietary zinc intake increases aluminum accumulation into the rat brain. *Brain Re*s 1983;288:393-395. Zinc deficiency will cause more aluminum to be absorbed into the body in general, and into the brain in particular. Aluminum will be absorbed by competing for binding sites on a zinc-containing ligand. Fluoride and phytates in soy formula will induce zinc deficiency.

1983
Poley JR and Klein AW. Scanning electron microscopy of soy protein-induced damage of

small bowel mucosa in infants. *J Pediatr Gastroenterol Nutr* 1983 May;2(2):271-87. Soy feeding caused damage to small bowel mucosa in 2 infants. The damage was similar to that of celiac disease and consistent with a lectin-induced toxicity.

1983
Tait S and others. The availability of minerals in food, with particular reference to iron. *Journal of Research in Society and Health*, April 1983;103(2):74?77. When precipitated soy products like tofu are consumed with meat, the mineral blocking effects of the phytates are reduced. The Japanese traditionally eat a small amount of tofu or miso as part of a mineral?rich fish broth, followed by a serving of meat or fish.

1983
Ross RK. Effect of in-utero exposure to diethylstilbesterol on age at onset of puberty and on post-pubertal hormone levels in boys," *Canadian Medical Association Journal* 1983, May 15;128(10):1197-8. Male children exposed during gestation to diethylstilbesterol (DES), a synthetic estrogen that has effects on animals similar to those of phytoestrogens from soy, had testes smaller than normal on maturation.

1984
Ologhobo AD and others. Distribution of phosphorus and phytate in some Nigerian varieties of legumes and some effects of processing. *Journal of Food Science*. January/February 1984;49(1):199-201. The phytic acid in soy is highly resistant to normal phytate-reducing techniques, such as soaking or long, slow cooking.

1994
Hawkins NM and others. Potential aluminium toxicity in infants fed special infant formula. *J Pediatr Gastroenterol Nutr* 1994;19(4):377-81 (1994). Researchers found aluminum concentrations of 534 micrograms/L in soy formula, as compared to 9.2 micrograms/L in breast milk. The authors concluded that infants may be at risk from aluminium toxicity when consuming formula containing more than 300 micrograms/L.

1985
Rackis JJ and others. The USDA trypsin inhibitor study. I. Background, objectives and procedural details. *Qualification of Plant Foods in Human Nutrition*, 1985;35. Diets of soy protein isolate high in trypsin inhibitors caused depressed growth and enlargement and pathological conditions of the pancreas, including cancer, and enlarged thryoid glands in rats. Analyses for this study showed that trypsin inhibitor content of soy protein isolate can vary as much as fivefold. Even low-level-trypsin-inhibitor SPI feeding resulted in reduced weight gain compared to controls. Soy protein isolate and textured vegetable protein made from soy protein isolate are used extensively in school lunch programs, imitation foods, commercial baked goods, diet beverages, meal replacements and fast food products. They are heavily promoted in Third World countries and form the basis of many food giveaway programs.

1986
McGraw MD and others. Aluminum content in milk formulae and intravenous fluids used in infants. *Lancet* I:157 (1986). Carefully collected human breast milk contained 5 to 20 micrograms aluminum per liter; concentrations were 10 to 20 fold greater in most cow's milk-based formulas and 100-fold greater in soy-based formulas.

1986
Fort P and others. Breast feeding and insulin-dependent diabetes mellitus in children. *J Am Coll Nutr* 1986;5(5):439-441. Twice as many soy-fed children developed diabetes as those in a control group that was breast fed or received milk-based formula. It was based on this study that the American Academy of Pediatrics took a position of opposition to the use of soy infant formula. This objection was later dropped after the AAP received substantial grants from the Infant Formula Council.

1986
Freni-Titulaer LW and others. *Am J Dis Child* 1986 Dec;140(12):1263-1267.Soy infant feeding was associated with higher rates of early development in girls, including breast development and pubic hair before the age of eights, sometimes before the age of three.

1987
Dabeka RW and McKenzie AD. Lead, cadmium, and fluoride levels in market milk and infant formulas in Canada. *J Assoc Off Anal Chem* 1987;70(4):754-7 (1987). Soy based or milk-free formulas contained about 8-15 times more cadmium than milk-based formulas as well as high amounts of fluoride.

1987
Katz SH. Food and Biocultural Evolution: A Model for the Investigation of Modern Nutritional Problems. *Nutritional Anthropology*, Alan R. Liss Inc., 1987, p 50. During the Chou Dynasty (1134 - 246 BC) the soybean was designated one of the five sacred grains, along with barley, wheat, millet and rice. However, the pictograph for the soybean, which dates from earlier times, indicates that it was not first used as a food; for whereas the pictographs for the other four grains show the seed and stem structure of the plant, the pictograph for the soybean emphasizes the root structure. Agricultural literature of the period speaks frequently of the soybean and its use in crop rotation. Apparently the soy plant was initially used as a method of fixing nitrogen. The soybean did not serve as a food until the discovery of fermentation techniques, sometime during the Chou Dynasty. Katz speculates that the rise of liver cancer in Africa is caused by the introduction of soy foods into the African diet.

1989
El Tiney A. Proximate Composition and Mineral and Phytate Contents of Legumes Grown in Sudan. *Journal of Food Composition and Analysis* 1989;2:67-68. Soybeans are listed as having some of the highest levels of phytic acid of all legumes. Phytic acid blocks the absorption of zinc, iron, copper and magnesium.

1989
Sandstrom and others. Effect of protein level and protein source on zinc absorption in humans. *J Nutr* 1989 Jan;119(1):48?53. When precipitated soy products like tofu are consumed with meat, the mineral blocking effects of the phytates are reduced. The Japanese traditionally eat a small amount of tofu or miso as part of a mineral?rich fish broth, followed by a serving of meat or fish.

1990
Campbell TC. *The Cornell-China-Oxford Project on Nutrition, Health and Environment*. 1990; Chen J and others. *Diet, Lifestyle and Mortality in China. A study of the characteristics of 65 counties*. Monograph, joint publication of Oxford University Press, Cornell University Press, China People's Medical Publishing House. 1990. This exhaustive study of Chinese diets found

that legume consumption ranged from 0 to 58 grams per day, with an average of 13 gams. Assuming that two-thirds of this is from soy beans, then consumption averages about 9 grams of soy products per day. Isoflavone content would probably be about 10 mg/day.

1990
Fort P and others. Breast and soy-formula feedings in early infancy and the prevalence of autoimmune thyroid disease in children. *J Am Coll Nutr* 1990;9:164-167. This study documents the association of soy formula feeding in infancy with autoimmune thryoid problems.

1990
Dabeka RW and McKenzie AD. Aluminium levels in Canadian infant formulate and estimation of aluminium intakes from formulae by infants 0-3 months old. *Food Addit Contam* 1990;7(2):275-82. Researchers found that aluminum content in soy formula for 1-3 month old infants could result in an intake of 363 micrograms/kg/day (2088 micrograms/day) alone, not including potential contribution from other foods or water.

1991
Hagger C and Bachevalier J. Visual habit formation in 3-month-old monkeys (Macaca mulatta): reversal of sex difference following neonatal manipulations of androgen. *Behavior and Brain Research* 1991, 45:57-63. Male infants undergo a "testosterone surge" during the first few months of life, when testosterone levels may be as high as those of an adult male. During this period, the infant is programed to express male characteristics after puberty, not only in the development of his sexual organs and other masculine physical traits, but also in setting patterns in the brain characteristic of male behavior. In monkeys, deficiency of male hormones impairs the development of spatial perception (which, in humans, is normally more acute in men than in women), of learning ability and of visual discrimination tasks (such as would be required for reading.)

1994
Messina MJ and others. Soy Intake and Cancer Risk: A Review of the In Vitro and In Vivo Data," *Nutrition and Cancer*, 1994, 21:(2):113-131. This study fueled speculation on soy's anticarcinogenic properties. The authors noted that in 26 animal studies, 65 percent reported protective effects from soy. At least one study was left out, in which soy feeding caused pancreatic cancer, the 1985 study by Rackis. In the human studies listed, the results were mixed. A few showed some protective effect but most showed no correlation at all between soy consumption and cancer rates. ". . the data in this review cannot be used as a basis for claiming that soy intake decreases cancer risk." In a subsequent book, The Simple Soybean and Your Health, Messina recommends 1 cup or 230 grams of soy products per day in his "optimal" diet as a way to prevent cancer.

1995
Chorazy PA and others. Persistent hypothyroidism in an infant receiving a soy formula: case report and review of the literature. *Pediatrics* 1995 Jul;96(1 Pt 1):148-50. the study describes a case of persistent hypothyroidism in an infant who had received soy formula.

1995
Anderson JW and others. Meta-analysis of the Effects of Soy Protein Intake on Serum Lipids. *New England Journal of Medicine*, 1995 333:(5):276-82. The FDAs allowance of a health claim for soy protein is based largely on this meta-anaylsis, sponsored by Protein

Technologies International. However, the study authors discarded eight studies for various reasons, leaving a remainder of 29. The published report suggested that individuals with cholesterol levels over 250 mg/dl would experience a "significant" reduction of 7 to 20 percent in levels of serum cholesterol if they substituted soy protein for animal protein. Cholesterol reduction was insignificant for individuals whose cholesterol was lower than 250 mg/dl. In other words, for most of the population, the substitution of meat with soy will not bring blood cholesterol levels down.

1996
Harras A, ed. *Cancer Rates and Risks*, 4th Edition, 1996, National Institutes of Health, National Cancer Institute. This report shows that the Japanese, and Asians in general, have lower rates of breast and prostate cancer but much higher rates of other types of cancer, particularly cancer of the esophagus, stomach, pancreas and liver.

1996
Fukutake M and others. Quantification of genistein and genistin in soybeans and soybean products. *Food Chem Toxicol* 1996;34:457-461. Average isoflavone consumption in Japan was found to be about 10 mg per day.

1997
IEH assessment on Phytoestrogens in the Human Diet, Final Report to the Ministry of Agriculture, Fisheries and Food, UK, November 1997. This exhaustive report on phytoestrogens, prepared by the British government, failed to find much evidence of benefit and warned against potential adverse effects.

1997
Herman-Giddens ME and others. Secondary Sexual Characteristics and Menses in Young Girls Seen in Office Practice: A Study from the Pediatric Research in Office Settings Network. *Pediatrics*, 1997 Apr;99:(4):505-512. Investigators found that one percent of all girls now show signs of puberty, such as breast development or pubic hair, before the age of three; by age eight, 14.7 percent of white girls and almost 50 percent of African-American girls had one or both of these characteristics. Our Comment: The widespread use of soy-based formula, beginning in the 1970s, is a likely explanation for the increase in early maturation in girls.

1998
Nagata C and others. Decreased serum total cholesterol concentration is associated with high intake of soy products in Japanese men and women. *J Nutr* 1998 Feb;128(2):209-13. This study included a survey of soy consumption among Japanese men and women. Consumption of soy products was about 54 grams per day for women and 64 grams per day for men. The total amount of soy protein from these products was 7-8 grams providing about 25 mg isoflavones.

1998
Irvine CH and others. Phytoestrogens in soy-based infant foods: concentrations, daily intake and possible biological effects. *Proc Soc Exp Biol Med* 1998 Mar;217(3):247-53. Researchers found that soy formulas provide infants with a daily dose rate of 3 mg/kg body weight total isoflavones, "which is maintained at a fairly constant level between 0-4 months of age. . . . This rate of isoflavone intake is much greater than that shown in adult humans to alter reproductive hormones."

1998
Yaffe K and others. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. *J Am Geriatr Soc* 1998 Jul;46(7):918-20. Women in the higher estrone quartiles had lower performance on two cognitive tests.

1998
Irvine CH and others. Daily intake and urinary excretion of genistein and daidzein by infants fed soy- or dairy-based infant formulas. *Am J Clin Nutr* 1998 Dec;68(6 Suppl):1462S-1465S. Researchers found that "young infants are able to digest, absorb, and excrete genistein and daidzein from soy-based formulas as efficiently as do adults consuming soy products.

1999
Eklund G and Oskarsson A. Exposure of cadmium from infant formulas and weaning foods. *Food Addit Contam* 16(12):509-19 (1999). Cadmium was 6 times higher in soy formulas than cow's milk formulas.

1999
Olguin MC and others. Intestinal alterations and reduction of growth in prepuberal rats fed with soybean [Article in Spanish]. *Medicina* (B Aires) 1999;59:747-752. Rats fed soy-based chow had reduced growth and an increase in gastrointestinal problems compared to controls.

1999
Nilhausen K and Meinertz H. Lipoprotein(a) and dietary proteins: casein lowers lipoprotein(a) concentrations as compared with soy protein. *Am J Clin Nutr* 1999;69:419-25. Many studies have shown that soy consumption can lower serum cholesterol levels. These studies have led to claims that soy can prevent heart disease. However, the theory that high cholesterol levels cause heart disease is becoming more and more untenable. Cholesterol levels are not a good marker for proneness to heart disease. However Lipoprotein(a) or Lp(a), does serve as a good marker for heart disease. This study indicates that soy raises Lp(a), meaning that it is likely to contribute to heart disease.

1999
Food Labeling: Health Claims: Soy Protein and Coronary Heart Disease, Food and Drug Administration 21 CFR Part 101 (Docket No. 98P-0683). This US government document allows a health claim for foods containing 6.25 grams of soy protein per serving. The original petition, submitted by Protein Technologies International (a division of Dupont), requested a health claim for isoflavones, the estrogen-like compounds found plentifully in soybeans, based on assertions that "only soy protein that has been processed in a manner in which isoflavones are retained will result in cholesterol-lowering." In 1998, the FDA made the unprecedented move of rewriting PTI's petition, removing any reference to the phytoestrogens and substituting a claim for soy protein, a move that was in direct contradiction to the agency's regulations. The FDA is authorized to make rulings only on substances presented by petition. The abrupt change in direction was no doubt due to the fact that a number of researchers, including scientists employed by the US government, submitted documents indicating that isoflavones are toxic. The regulations stipulate that 25 grams of soy protein per day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. Twenty-five grams soy protein can contain from 24-125 mg isoflavones, depending on processing methods. Many letters were written in protest,

expressing concerns about mineral blocking effects, enzyme inhibitors, goitrogenicity, endocrine disruption, reproductive problems and increased allergic reactions from consumption of soy products.

1999
Sheehan DM and Doerge DR, Letter to Dockets Management Branch (HFA-305) February 18, 1999. A strong letter of protest from two government researchers at the National Center for Toxicological Research urging that soy protein carry a warning label rather than a health claim.

1999
Ginsburg J and Prelevic GM. Is there a proven place for phytoestrogens in the menopause?" *Climacteric*, 1999;2:75-78. Quantification of discomfort from hot flashes is extremely subjective and most studies show that control subjects report reduction in discomfort in amounts equal to subjects given soy.

1999
White L. Association of High Midlife Tofu Consumption with Accelerated Brain Aging. Plenary Session #8: Cognitive Function, The Third International Soy Symposium, Program, November 1999, page 26. An ongoing study of Japanese Americans living in Hawaii found a significant statistical relationship between two or more servings of tofu per week and "accelerated brain aging." Those participants who consumed tofu in mid life had lower cognitive function in late life and a greater incidence of Alzheimer's and dementia.

2000
Clarkson TB. Soy phytoestrogens: what will be their role in postmenopausal hormone replacement therapy? *Menopause* 2000 Mar-Apr;7(2):71-5. Soy did not prevent bone loss when measured at autopsy in female monkeys who had had their reproductive organs removed.

2000
Vincent A and Fitzpatrick LA. Soy isoflavones: are they useful in menopause? *Mayo Clin Proc* 2000;75:1174-84. "Current data are insufficient to draw definitive conclusions regarding the use of isoflavones as an alternative to estrogen for hormone replacement in postmenopausal women."

2000
North K and Golding J. A maternal vegetarian diet in pregnancy is associated with hypospadias. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *BJU Int* 2000 Jan;85(1):107-113. Vegetarian women are more likely consume more soy than the general population. Incidence of hypospadias was twice as great in vegetarian mothers than in nonvegetarian mothers. Hypospadias is a birth defect due to interrupted development of the penis.

2000
Nakamura Y and others. Determination of the levels of isoflavonoids in soybeans and soy-derived foods and estimation of isoflavonoids in the Japanese daily intake. *J AOAC Int* 2000;83:635-650. This survey found that average isoflavone consumption in Japan is about 28 mg per day.

2000
Bee G. Dietary Conjugated Linoleic Acids Alter Adipose Tissue and Milk Lipids of Pregnant and Lactating Sows. *J Nutr* 2000;130:2292-2298. Dietary mixtures for pigs, which are carefully formulated to promote reproduction and growth, allow approximately 1 percent of the ration as soy in a diet based on grains and supplements. (Pigs have a digestive system similar to humans.) The Central Soya Company, Inc. website gives a range of 2.5 percent to 17.5 percent soy in the diet of pigs, citing a number of anti-nutritional components that "have been documented to cause gastrointestinal disturbance, intestinal damage, increased disease susceptibility and reduced performance in pigs."

2000
Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *International Journal of Epidemiology* Oct 2000; 29(5):832-6. This study contained the following official conclusion: "The present study provides modest support for the preventive role of soy against stomach cancer and heart disease death." However, only the association with lower heart disease death is correct. What the study actually found was that "Soy protein intake was significantly correlated with stomach cancer mortality rate in men" and "soy product intake estimated as total amount as well as isoflavone and soy protein intake were significantly positively correlated with colorectal cancer mortality rates in both sexes." In other words, men who consumed lots of soy had more stomach cancer and men and women who consumed lots of soy had more colorectal cancer. These results are especially interesting as soy proponents often claim that Asians have lower rates of colorectal cancer because they eat more soy.

2001
Strom BL and others. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA* 2001 Nov 21;286(19):2402-3. Although reported in the media as a vindication of soy infant formula, the study actually found that soy-fed infants had more reproductive problems and more asthma as adults.

2001
Massey LK and others. Oxalate content of soybean seeds (Glycine max: Leguminosae), soyfoods, and other edible legumes. *J Agric Food Chem* 2001 Sep;49(9):4262-6. Soy foods were found to be high in oxalates and likely to contribute to kidney stones.

2002
Khalil DA and others. Soy protein supplementation increases serum insulin-like growth factor-I in young and old men but does not affect markers of bone metabolism. *J Nutr* 2002 Sep;132(9):2605-8. Men consuming soy protein had higher levels of insulin-like growth factor-I (IGF-I) than those consuming milk protein. According to many other studies (but not stated in the report), high levels of IFG-I are also found in rBGH milk and have been implicated in causing hormonal cancers.

2003
Lack G and others. Factors associates with the development of peanut allergy in childhood. *N Engl J Med* 2003 Mar 13;348(11):977-85. The number of children with life-threatening peanut allergies has tripled during the last decade. This study suggests a link between consumption of soy-based formula and the development of peanut allergies. Scientists at the University of Bristol monitored 14,000 babies in the southwest of England. Among the 49 children who developed a peanut allergy, almost a quarter had consumed soy milk

during their first two years. (Less than 5 percent of babies overall receive soy formula in the UK.) According to lead researcher Gideon Lack, "These results suggest that sensitization to peanut may possibly occur. . . as a result of soya exposure."